UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,004	02/12/2001	Bassil I. Dahiyat	067461-5041-US01	1900

67374   7590   07/22/2008

MORGAN, LEWIS & BOCKIUS, LLP
ONE MARKET SPEAR STREET TOWER
SAN FRANCISCO, CA 94105

EXAMINER
BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
07/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS,
WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed
  after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
  Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any
  earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2008*.
2a)☒ This action is **FINAL**.   2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is
closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-41* is/are pending in the application.
    4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *36-41* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
    a)☐ All   b)☐ Some * c)☐ None of:
        1.☐ Certified copies of the priority documents have been received.
        2.☐ Certified copies of the priority documents have been received in Application No. _____.
        3.☐ Copies of the certified copies of the priority documents have been received in this National Stage
            application from the International Bureau (PCT Rule 17.2(a)).
    * See the attached detailed Office action for a list of the certified copies not received.

DETAILED ACTION

Status of Claims

1.   Amendment filed 04/15/2008   is acknowledged.

Claims 36-41 are pending. Claim 36 is amended.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly
claiming the subject matter which the applicant regards as his invention.

The rejections under 35 U.S.C. 112, second paragraph, previously applied to

claims 36-41 are hereby withdrawn in view of amendments to the claims and applicant's

comments.

The following rejection is necessitated by amendment.

2.   Claims 36-41 are rejected under 35 U.S.C. 112, second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Claim 36 as amended recites that "at least one

member of said secondary library comprises a plurality of variable amino acids relative

to said target protein" (step ii). It is not clear what are "variable amino acids" as this

term is not defined in the specification (specification is using term "variable positions"

instead).

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 36 is amended to recite that "at least one member of said secondary library comprises a plurality of variable amino acids relative to said target protein" (step ii). First, there is no disclosure in the specification on the meaning and scope of the definition of "variable amino acids" - specification is using term "variable positions". Second, there is no disclosure in the specification of a "member of secondary library" that comprises a "plurality of variable amino acids" which amino acids are "relative to said target protein".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3.   Claims 36-41 are rejected 35 U.S.C. 103(a) as being unpatentable over Wang et al (Protein Engineering, 9 (6), 479-484, 1996) and Dahiyat,1997 (J. Mol. Biol., 1997, 273, 789-796).

The claims are directed to method for generating of at least one non-naturally occurring variant protein with at least one desired characteristic relative to a target protein comprising:

a)   inputting the coordinates of said target protein into a computer;

b)   identifying a list of variable residue positions in said target protein based upon said at least one desired characteristic

c)   applying a force field calculation to said variable residue positions to generate a primary library comprising optimized variant protein sequences;

d)   generating a set of amino acid residues at each of said variable residue positions by combining:

- (i) at least one variant amino acid in said primary library at said variable residue position, and

- (ii) the amino acid residue of said target protein at said variable residue position;

e)   generating a plurality of protein sequences by combining into the sequence of said target protein each of said set of amino acid residues at each of said variable residue positions to generate a secondary library of protein sequences, wherein at least one member of said secondary library is not found in said primary library; and

f)   synthesizing a plurality of said secondary library protein sequences and

screening said sequences to identify at least one non-naturally occurring variant protein

with said at least one desired characteristic.

Wang et al teach use of force field to design protein variants. Based on protein

main chain characteristics, the mean force field was constructed to evaluate the

compatibility between an amino acid residue and its environment, from which a position-

dependent protein mutant profile was constructed. At each position along a protein

sequence, the native residue was replaced by the other 19 types of amino acid

residues. The reference concludes that creating such libraries can be used as a guide in

protein engineering and as an effective scoring matrix in protein sequence–structure

alignment studies.

In particular the method comprises the following steps which are correlated to

the steps of the instant method as follows:

Instant claim 36	Wang et al
a) inputting the coordinates of said target protein into a computer;	See p. 479, bottom.
b) identifying a list of variable residue positions in said target protein based upon said at least one desired characteristic	In Wang's case, all residues are "variable". see obviousness part of rejection below. In addition, "variable" positions can be further identified by using force field calculations as the "mutant profile can

	point out at which positions along the sequence the mutation is forbidden" (p. 483, last paragraph)
c) applying a force field calculation to said variable residue positions to generate a primary library comprising optimized variant protein sequences;	For each residue in the sequence, Wang applies force field calculation to 19 other natural amino acid residues. This is viewed as generating a "primary library" – see Fig. 1
d) generating a set of amino acid residues at each of said variable residue positions by combining: • (i) at least one variant amino acid in said primary library at said variable residue position, and • (ii) the amino acid residue of said target protein at said variable residue position, and e) generating a plurality of protein sequences by combining into the sequence of said target protein each of	Fig 1 in Wang compiles sequences obtained by generating sets of residues for each "variable residue" in the order of energy efficiency and recombining them into sequences in the order of sequence of the original protein. Even though Wang does not teach directly which of the proteins is to be generated, it states that "the predicted mutant profile can act as a guide for protein engineering. " (p. 483, last paragraph). Thus, it would be obvious to combine the residues

| said set of amino acid residues at each of said variable residue positions to generate a secondary library of protein sequences, wherein at least one member of said secondary library is not found in said primary library | indicated by force field calculations as being suitable and being low energy and using permutations of such "optimal" residues", to generate a library of optimized sequences (i.e., a "secondary" library).

 Since for each position Fig. 1 comprises both the substituted residues (i.e., residues from "primary library") and the native residue, it results in a set as per step d), and a library as per step e). Since the latter library is comprised of sequences comprises native residues in addition to mutant residues in "primary" library, it is different in at least one member from the library comprised only of mutant residues. |

Wang does not teach identifying particular residues based upon said at least one desired characteristic. However, it would be obvious to one skilled in the protein modeling art that mutation of all residues of target protein would be exhaustive and useless and it will completely obliterate the functions of the original protein. Usually

performed is such modifying of residues that seem to be beneficial. see, for example Dahiyat, 1997. When there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Thus, Examiner consider obvious first identifying particular residues of interest in the method of Wang et al.

Further, Wang et al does not explicitly teach synthesizing a plurality of protein sequences and screening their activity. However, it would be obvious to one skilled in the art that the desirable end stage of any protein modeling is synthesis of proteins of interest and verifying its desirable functions.

Further, with regard to claims 37-41, selection of PCR method to synthesize proteins would be obvious to an artisan as it is one of the main methods of protein synthesis, and selection of particular parameters of PCR would be obvious to an artisan as a part of routine selection of optimal parameters.

Response to arguments

Applicant argues that Wang does not teach or suggest generation of a "secondary library". In response, even though Wang does not teach directly which of the proteins is to be generated, it states that "the predicted mutant profile can act as a guide for protein engineering. " (p. 483, last paragraph). Thus, it would be obvious to combine the residues indicated by force field calculations as being suitable and being

low energy and using permutations of such "optimal" residues", to generate a library of

optimized sequences (i.e., a "secondary" library).

Further, applicant argues that members of secondary library have plurality of

variant amino acids "relative to the target protein". In response, any sequence in Fig. 1

is viewed as having have plurality of variant amino acids "relative to the target protein",

as it has a plurality of substitutions being relative to the original residue in the same

position.

Further, applicant argues that the reference does not teach using force field to

generate a secondary library. In response, the instant claims do not require using force

field to generate a secondary library; rather, the claims are directed to using force field

to generate a primary library, and this is what is being described in the reference.

Conclusion.

6.   No claims are allowed

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Michael Borin whose telephone number is (571) 272-

0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number

for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent
Application Information Retrieval (PAIR) system. Status information for published
applications may be obtained from either Private PAIR or Public PAIR. Status
information for unpublished applications is available through Private PAIR only. For
more information about the PAIR system, see http://pair-direct.uspto.gov. Should you
have questions on access to the Private PAIR system, contact the Electronic Business
Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO
Customer Service Representative or access to the automated information system, call
800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./
Primary Examiner, Art Unit 1631